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SUBSTANTIATION OF THE FILM-FORMING AGENT SELECTION IN THE COMPOSITION OF SPRAY WITH COPPER AND SILVER CITRATE

Topicality. Mastitis continues to be the most common disease of dairy cows. In order to prevent the infection of the mammary gland in cows, the udders were treated with a suitable disinfectant, by spraying or full immersion in the preparation.

Aim of this work the choice of a film-forming agent in the composition of copper and silver citrates containing spray and the effect of the film-forming agent on the quality parameters of the antiseptic agent.

Materials and methods. As the research objects have been selected: film-forming agent: sodium carboxymethyl cellulose (CMC), macrogol-400, polyquaternium 10. The quantitative content of silver ions in the spray was determined thiocyanometric measurement. The quantitative content of copper ions, dexpantenol; potentiometric determination of pH and statistical analysis of the results was carried out in accordance with the requirements of the S.Ph.U.

Results and discussion. Samples of CMC-containing spray 0.3 %, 0.5 % and 1 % were sticky and formed a thick film which did not meet the requirements of normative and technical document (NTD) in terms of "Relative density". The conducted studies allowed us to conclude that it is inappropriate to introduce macrogol-400 as a film-forming agent in an amount from 10 % to 20 % into the composition of the combined spray for the veterinary use. Spray obtained with its use form very thin film, and when applied to the skin is washed out quickly. In addition, the samples do not meet the requirements of the NTD.

Conclusions. It has been established that the optimum film-forming agent in composition of antiseptic spray is polyquaternium 10 in the amount of 0.5 %, which allowed to obtain a film with predictable properties, and the preparation itself meets the requirements of the design developed by the normative and technical documentation for all indicators of quality.

Key words: *veterinary drug; antiseptic spray; film-forming agent; copper and silver citrate*

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Обґрунтування вибору плівкоутворювача у складі спрею з цитратами міді та срібла

Актуальність. Мастит великої рогатої худоби продовжує залишатися найбільш поширеним захворюванням молочних корів. З метою профілактики інфікування молочної залози у корів дійки вимені обробляють підходящим дезінфектантом шляхом обприскування або повного занурення в засіб.

Мета роботи. Обґрунтування вибору плівкоутворювача у складі спрею з цитратами міді та срібла і вплив плівкоутворювача на показники якості антисептичного засобу.

Матеріали та методи. Як об'єкти дослідження обрані натрію карбоксиметилцелюлоза (КМЦ), макрогол-400 та полікватерніум 10. Кількісний вміст іонів срібла визначали тіоціанометрично. Кількісний вміст іонів міді, декспантенолу, потенціометричне визначення рН та статистичну обробку результатів проводили згідно з методикою ДФУ (2.0).

Результати та їх обговорення. Дослідження показали, що використання КМЦ в концентрації 0,3 % дозволяє отримати спреї з рН 2,16 з допустимим рівнем кількісного вмісту діючих речовин, який утворює дуже тонку плівку, що не задовольняє передбачуваним характеристикам. Також проведені дослідження дозволили зробити висновок про недоцільність введення до складу комбінованого спрею макроголу-400 в кількості від 10 % до 20 %. Спреї, отримані з його використанням, при нанесенні на шкіру утворюють дуже тонку плівку, яка швидко змивається. Крім того, зразки не відповідають вимогам НТД за показником «Відносна густина». Використання полікватерніуму-10 з концентрацією 0,2 % утворює дуже тонку захисну плівку, а з концентрацією полікватерніуму-10 1 % одержують густий спреї, який висихає на шкірі, утворюючи надто щільну плівку, крім того, зразки цих серій спрею не відповідають вимогам НТД.

Висновки. Встановлено, що оптимальним плівкоутворювачем у складі антисептичного спрею є полікватерніум-10 у кількості 0,5 %, що дозволило одержати плівку з передбачуваними властивостями, а сам препарат відповідає вимогам проекту розробленого НТД за усіма показниками якості.

Ключові слова: *ветеринарний препарат; спреї антисептичний; плівкоутворювач; міді та срібла цитрат*

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Обоснование выбора пленкообразователя в составе спрея с цитратом меди и серебра

Актуальность. Мастит крупного рогатого скота продолжает оставаться наиболее распространенным заболеванием молочных коров. С целью профилактики инфицирования молочной железы у коров соски вымени обрабатывают подходящим дезинфектантом путем опрыскивания или полного погружения в средство.

Цель работы. Обоснование выбора пленкообразователя в составе спрея с цитратами меди и серебра и влияние пленкообразователя на показатели качества антисептического средства.

Материалы и методы. В качестве объектов исследования были выбраны пленкообразователи: натрия карбоксиметилцеллюлоза (КМЦ), макрогол-400, и поликватерниум-10. Количественное содержание ионов серебра определяли тиоцианометрично. Количественное содержание ионов меди, декспантенола, потенциометрическое определение рН и статистическую обработку результатов проводили согласно методик ГФУ (2.0).

Результаты и их обсуждение. Исследования показали, что использование КМЦ в концентрации 0,3 % позволяет получить спрей с pH 2,16 с допустимым уровнем количественного содержания действующих веществ, который образует очень тонкую пленку, не удовлетворяющую предполагаемым характеристикам. Также проведенные исследования позволили сделать вывод о нецелесообразности включения в состав комбинированного спрея макрогола-400 в количестве от 10 % до 20 %. Спреи, полученные с его использованием, при нанесении на кожу образуют очень тонкую пленку, которая быстро смывается. Кроме того, образцы не соответствуют требованиям НТД по показателю «Относительная плотность». Использование поликватерниума-10 с концентрацией 0,2 % образует очень тонкую защитную пленку, а с концентрацией поликватерниума-10 1 % получают густой спрей, который высыхает на коже, образуя слишком плотную пленку, кроме того, образцы этих серий спрея не соответствуют требованиям НТД.

Выводы. Установлено, что оптимальным пленкообразователем в составе антисептического спрея является поликватерниум 10 в количестве 0,5 %, что позволило получить пленку с желаемыми свойствами, а сам препарат соответствует требованиям проекта разработанного НТД по всем показателям качества.

Ключевые слова: ветеринарный препарат; спрей антисептический; пленкообразователь; меди и серебра цитрат

INTRODUCTION

The milk yield of cows and the quality of milk are important indicators for the successful development of animal cattle breeding and the economies of different countries. The most important parameters in the assessment of the quality of milk and its suitability for processing are the microbiological safety and the quantity of somatic cells contained in it. After all, mastitis continues to be the most common disease of dairy cows [1].

The main problems in ensuring the safety of milk include the lack of proper level of veterinary and sanitary control; process of production, processing, transportation and sale of milk and dairy products (from farm to consumers); insufficient conducting of medical-preventive, diagnostic measures aimed at the elimination and prevention of diseases of the mammary gland and reproductive organs of bovine animals; non-compliance with sanitary and hygiene norms and requirements. Infected milk is a source of a number of diseases, such as salmonellosis, staphylococcal enterotoxin gastroenteritis, streptococcal infections, typhoid fever, cholera, aftosa, brucellosis, leukemia and tuberculosis [2, 3].

Mastitis prevention is carried out by methods aimed at reducing the incidence and duration of infection. In order to prevent the infection of the mammary gland in cows, the udders were treated with a suitable disinfectant, by spraying or full immersion in the preparation [4, 5].

Modern effective formulations for cattle are present on the European market [6]. DeLaval (Sweden) is a leading manufacturer of milking processes automation equipment and other technological processes for dairy farms. The Company's concept of "productive lifetime of cows" requires innovative scientific approaches to the milking procedure. The experience of the company proved that the treatment of the udder after milking being the most effective method of mastitis prophylaxis [7]. Also, DeLaval's modern tools for udder handling are the components that prevent negative effects of the environment and mechanical effects on the skin of the udder. On farms, before the introduction of preparations for disinfection of udder into practice, in 80 % of cases there was a staphylococcus aureus identified on the surface of the udder. Blockade™ is a film-forming iodine-based solution for applying dyes, in which free iodine is used. The Blockade™ solution creates a thin, elastic barrier for the natural bac-

teria that present in the dirt and that can enter the milk channel, especially after milking. Dipping the nipples into the Blockade solution after each milking provides the formation of a protective film [8, 9].

Proactive™, Proactiv™ Plus, Dipal™ Conc., IodoFence™, iodine-based preparations; DeLaval Prima contains hydrogen peroxide; Hamra Blue™ – chlorhexidine bigluconate [10]. The formulas of these agents prevent the infection of the animal's udder by a wide range of microorganisms that cause mastitis. Unfortunately, these drugs have a high cost for consumers in Ukraine [11].

Previous studies have established the price parameters for foreign veterinary preparations with anti-mastitis activity significantly exceed the similar indices for domestic preparations. The analysis conducted by us proves that the development of a new preparation for the antiseptic treatment of ducts and udder of cattle in order to prevent microbial contamination is economically feasible [12]. We also studied the antimicrobial activity of silver and copper citrates in order to develop veterinary antimicrobial agents [13, 14]. This work is a continuation of the scientific experiment with the aim of substantiating the choice of a film-forming agent in the composition of copper and silver citrates containing spray and the effect of the film-forming agent on the quality parameters of the antiseptic agent.

MATERIALS AND METHODS

As a research objects, a series of preparations with different composition, were developed. The following active substances were used: silver and copper citrate (manufacturer of Ltd. "Nanomaterials and nanotechnologies", Kyiv); D-panthenol USP (BASF SE, Germany); and excipients. We used sodium carboxymethyl cellulose (Shandong YuLong, China), macrogol-400 (Kollisol® PEG 400, BASF SE, Germany) and polyquaternium 10 (East Korea, KCI) in our studies on film-forming agent selection.

The quantitative content of silver ions in the spray was determined thiocyanometric measurement [15]. Quantitative content of copper ions was performed according to the methodology of the State Pharmacopoeia of Ukraine 2.0 (S.Ph.U.) "2.2.25 Absorption spectrophotometry in the ultraviolet and visible range". The quantitative determination of dexpanthenol was carried out by liquid chromatography according to the procedure of the S.Ph.U.

"2.2.29. Liquid chromatography". Potentiometric determination of pH in experimental samples was carried out using the method of DFU 2.0, paragraph 2.2.3. The measurements were carried out using the pH meter Seven Easy pH with a set of electrodes manufactured by Mettler Toledo (China). Statistical processing of the experimental data results was carried out in accordance with the requirements of the S.Ph.U., article 2.0 "5.3.N.1. Statistical analysis of the results of a chemical experiment" [16].

RESULTS AND DISCUSSION

According to the S.Ph.U. "Veterinary liquid drugs for skin application": sprays contain one or more active substances for external use for therapeutic or prophylactic purposes. They are extracted in the form of aerosols by pressing on the corresponding valve or by means of an appropriate spray device, which is either an integral part of the container or supplied separately. In turn, sprays for nipples contain one or more disinfectant active substances, usually in the form of solutions spraying onto the nipple of animals before and, if necessary, after milking of milk to reduce the amount of pathogenic microorganisms on the surface.

Auxiliary substances in the veterinary sprays (solvents, surfactants, film formers, corrective agents, antimicrobial preservatives, antioxidants, etc.) should provide optimum technological characteristics of the veterinary preparation, be compatible with other components of the medicinal form and the packaging material [17].

In developing the composition of the spray for veterinary on the basis of silver citrate and copper, studies were conducted to select the optimum film formulation for this dosage form. In the pharmaceutical technology, copolymers such as vinyl pyrrolidone with vinyl acetate, cellulose acetate butyrate, polyquaternium, povidone, macrogol-400, sodium carboxymethyl cellulose (CMC) and others are used as a film-forming agents. Substances in the form of a veterinary preparation for the application of the skin should not irritate the skin of the animal, and should be non-toxic. The formed film must be impermeable to microorganisms, elastic, durable, have a high degree of adhesion, and possess high bacteriostatic properties. The advantages of film-forming agents in the composition of the preparation for the antiseptic treatment of dentures and vines of the cattle which include protection of the dama-

ged skin surface from infection.

As a result of the experiment, formulations of antiseptic spray containing carboxymethyl cellulose in various concentrations as a film-forming agent, were developed. Carboxymethyl cellulose is an amorphous substance without color, taste or smell, well soluble in water, has the weak acidic properties, does not decompose under the light and forms films that are resistant to fats of plant and animal origin. The advantage of carboxymethyl cellulose (CMC) is that this substance is physiologically inert.

The results of the research on the selection of optimal amounts of CMC are presented in Tab. 1.

From the data in Tab. 1 it can be seen that the use of CMC at a concentration of 0.3 % allows obtaining of spray with a pH of 2.16, and a permissible level of quantitative content of active substances, which forms a very thin film that does not satisfy the predicted characteristics. Samples of CMC-containing spray 0.5 % and 1 % were sticky and formed a thick film which did not meet the requirements of normative and technical document in terms of "Relative density".

Therefore, the next step was the development of antiseptic preparation batches with macrogol-400 film-forming agent. Macrogol-400 is well mixed with water, glycerol, organic solvents, compatible with most medicinal substances, it is well applied to the skin and uniformly distributed on it without interfering with gas exchange and without disturbing the activity of the glands; it also retains homogeneity after mixing with secretions of the skin or mucous membrane; has a weak bactericidal effect due to the presence of primary hydroxyl groups in the molecule; is not exposed to microorganisms and can be stored for quite a long time under any temperature conditions.

The results of research on the choice of optimal quantities of macrogol-400 are presented in Tab. 2.

The conducted studies allowed us to conclude that it is inappropriate to introduce macrogol-400 as a film-forming agent in an amount from 10 % to 20 % into the composition of the combined spray for the veterinary use. Spray obtained with its use form very thin film, and when applied to the skin is washed out quickly. In addition, the samples do not meet the requirements of the normative and technical documentation in terms of "Relative density".

Table 1

DEPENDENCE OF SPRAY QUALITY INDICATORS ON THE BASIS OF SILVER AND COPPER CITRATES FROM THE QUANTITY OF CARBOXYMETHYLCELLULOSE (CMC)

CMC content, %	Film characteristics	Quality parameters					
		Appearance (opaque blue-greenish color liquid)	Relative density, g/cm ³ (from 1.016 to 1.018)	pH (2.0-5.0)	Quantitative content, %		
					Argentum ions (not less than 0.0113)	Copper ions (not less than 0.0113)	Dexpanthenol (4.75-5.25)
0,3	very thin	complies	complies	2.13 ± 0.03	0.0126 ± 0.0001	0.0127 ± 0.0002	5.00 ± 0.01
0.5	sticky, thick	complies	does not comply	2.15 ± 0.02	0.0127 ± 0.0003	0.0127 ± 0.0002	5.00 ± 0.02
1.0	sticky, thick	complies	does not comply	2.16 ± 0.02	0.0126 ± 0.0002	0.0127 ± 0.0001	5.02 ± 0.03

Note: P ± 95 %, n = 5.

Table 2

**THE DEPENDENCE OF SILVER AND COPPER CITRATES BASED SPRAY QUALITY INDICATORS
ON THE QUANTITY OF MACROGOL-400**

Macrogol-400 quantity, %	Film characteristics	Quality parameters					
		Appearance (opaque blue- greenish color liquid)	Relative density, g/cm ³ (from 1.016 to 1.018)	pH (2.0-5.0)	Quantitative content, %		
					Argentum ions (not less than 0.0113)	Copper ions (not less than 0.0113)	Dexpanthenol (4.75-5.25)
10.0	very thin	complies	complies	2.13 ± 0.01	0.0127 ± 0.0001	0.0129 ± 0.0002	4.99 ± 0.01
15.0	very thin	complies	does not comply	2.15 ± 0.01	0.0128 ± 0.0002	0.0128 ± 0.0001	4.98 ± 0.02
20.0	very thin	complies	does not comply	2.13 ± 0.02	0.0126 ± 0.0003	0.0126 ± 0.0001	5.02 ± 0.01

Note: P ± 95 %, n = 5.

Table 3

**THE DEPENDENCE OF SILVER AND COPPER CITRATES BASED SPRAY QUALITY
INDICATORS ON THE QUANTITY OF POLYQUATERNIUM 10**

Quantity of polyquaternium 10, %	Film characteristics	Quality parameters					
		Appearance (opaque blue-greenish color liquid)	Relative density, g/cm ³ (from 1.016 to 1.018)	pH (2.0-5.0)	Quantitative content, %		
					Argentum ions (not less than 0.0113)	Copper ions (not less than 0.0113)	Dexpanthenol (4.75-5.25)
0.2	very thin	complies	does not comply	2.13 ± 0.01	0.0125 ± 0.0001	0.0126 ± 0.0001	5.09 ± 0.02
0.5	intermediate density	complies	complies	2.15 ± 0.01	0.0128 ± 0.0002	0.0128 ± 0.0001	4.99 ± 0.03
1.0	dense	complies	does not comply	2.16 ± 0.02	0.0126 ± 0.0001	0.0127 ± 0.0002	5.07 ± 0.01

Note: P ± 95 %, n = 5.

In the further development of the spray composition, there was used polyquaternium 10, a cationic derivative of hydroxyethyl cellulose which is widely utilized as a conditioning agent in hair and skin products. Polyquaternium 10 is compatible with anionic and amphoteric surfactants. It possesses film-forming property and creates a protective protective film on the skin and hair. The results of study on the choice of optimal quantities of polyquaternium 10 are presented in Tab. 3.

The use of polyquaternium 10 in a concentration of 0.5 % allows to obtain a spray with a pleasant texture, pH of 2.16, with an acceptable level of quantitative content of active substances. A sample prepared with a 0.2 % film-forming agent dried on the skin, forming a very thin protective film, and using a concentration of polyquaternium 10 of 1 %, a thick spray was obtained. It dries on the skin forming a dense film, and in addition samples of these series of sprays did not meet the requirements of normative and technical documentation in terms of "Relative density".

As a result of the research, it was found that the introduction into the composition of a combined antiseptic agent with copper and silver citrates for veterinary use, polyquaternium 10 in the amount of 0.5 %, allowed to obtain a spray that meets the requirements of the nor-

mative and technical documentation for all quality indicators, forming a protective film with intermediate density.

CONCLUSIONS

1. The studies have been conducted in order to substantiate the selection of a film-forming agent in the form of a spray containing copper and silver citrates for the antiseptic treatment of cattle for prevention of infection with microorganisms causing mastitis.
2. In development of the spray composition for veterinary medicine on the basis of silver and copper citrate the influence of film formers (sodium carboxymethyl cellulose, macrogol-400 and polyquaternium 10) on the quality indices of the antiseptic agent was studied.
3. It has been established that the optimum film-forming agent in composition of antiseptic spray is polyquaternium 10 in the amount of 0.5 %, which allowed to obtain a film with predictable properties, and the preparation itself meets the requirements of the design developed by the normative and technical documentation for all indicators of quality.

Conflict of Interests: authors have no conflict of interests to declare.

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